THESIS

submitted to the University of Glasgow

for the degree of Doctor of Philosophy

ON THE STRUCTURAL RELATIONSHIPS OF CERTAIN MEMBERS OF THE BICYCLIC SESQUITERPENE SERIES.

by

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THE SESQUITERPENE COMPOUNDS.

Ethereal oils are very widely distributed in the plant kingdom, but are confined almost exclusively to the phanerogams. What part they play in the life cycle of the plant is not yet known; they are commonly regarded as products of metabolism for which the plant has no further use. It seems probable, however, that they may play an important part in the economy of the living plant. cf. Bokorny (1899)[1] Cavel (1918)[2] Giglioli (1911)[3] Researches on various questions of physiological interest in connection with ethereal oils have been carried out by Charabot (1900-1908)[4,5] and others.

The oils themselves may be obtained from the plant by a variety of methods, such as pressing and steam distillation. When isolated, the oil usually consists of a very complex mixture of hydrocarbons, alcohols, and esters.

The terpenes, a large family of isomeric hydrocarbons of the formula $C_{10}H_{16}$, and their oxygenated derivatives, constitute an important part of many ethereal oils. Not less important are the sesquiterpenes, the $C_{15}H_{24}$ compounds; in some oils they are the most important constituents, while in nearly all they are present in sufficient quantity to have a pronounced effect on the properties of the oil. The chemistry of the sesquiterpenes

however, is much less advanced than that of the simple terpenes. Indeed, only quite recently have the structural relationships of these complex bodies been investigated with any success.

Together with the sesquiterpenes, $C_{15}H_{24}$, occur alcohols of the formulae $C_{15}H_{26}O$ and $C_{15}H_{24}O$, and a very few more highly oxygenated derivatives. As the oxygenated compounds may for purposes of classification be regarded as derivatives of the hydrocarbons, attention may be confined to the latter bodies in the first instance.

The sesquiterpenes are usually viscous liquids which boil about 100° higher than the ordinary terpenes. They are even more liable to intramolecular change than the latter bodies, especially under the influence of acids. Therefore the crystalline additive products which are in many cases formed with the halogen acids, and which afford such a convenient method of isolation, do not in all cases contain the same ring structure as the parent hydrocarbon. The most reliable method for determining the number of carbon rings in the molecule is afforded by the results of controlled catalytic reduction to a saturated hydrocarbon. Thus, the open chain members may be reduced to simple $C_{15}H_{32}$ hydrocarbons, the monocyclic to $C_{15}H_{30}$, the bicyclic to $C_{15}H_{28}$, and the tricyclic to $C_{15}H_{26}$ hydrocarbons. There are no known tetracyclic members, i.e. none of the

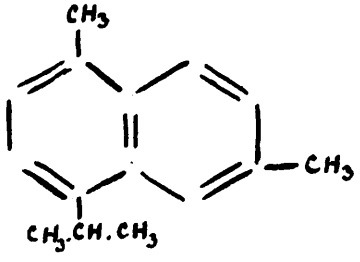
natural sesquiterpenes are saturated hydrocarbons.
On the basis of these results, confirmed by the molecular refractivity value, and other physical measurements, the sesquiterpenes may be divided conveniently into four groups with the following properties.

$C_{15}H_{24}$	d	n_D	Mol.Refr.
1.Tricyclic $\bar{\Gamma}1$	about 0.93-0.91	1.50-1.49	64.4
2.Bicyclic $\bar{\Gamma}2$	" 0.92-0.90	1.51-1.50	66.1
3.Monocyclic $\bar{\Gamma}3$	" 0.837	1.49	67.8
4.Aliphatic $\bar{\Gamma}4$	" 0.84	1.53	69.5

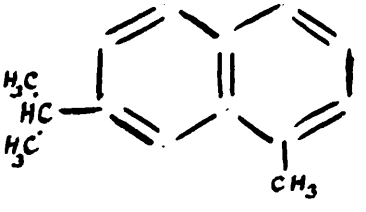
This classification was first advanced by Schreiner and Kremer (1901,1903)[6] and has been extended later, cf. Ruzicka, Meyer,and Mingazzini (1922)[7] .

As to the structure of these compounds, Wallach (1887)[8] had early suggested that the polycyclic sesquiterpenes might contain a hydrogenated naphthalene ring structure, and this excellent working hypothesis was elaborated by Semmler (1903)[9] . However, the oxidation experiments which in the case of the terpenes had yielded such brilliant results, when applied to the sesquiterpenes were not so successful and very few definite products

could be obtained. A possible explanation of this is is discussed on p. . Thus no definite evidence in support of the theory of a hydrogenated naphthalene structure was forthcoming until the work of Ruzicka and his collaborators commenced in this field in 1919. They were able to make a distinct advance by a method which had not been used at all with the simple terpenes. Ruzicka showed that by dehydrogenation with sulphur a great many of the sesquiterpene compounds yielded one or other of two naphthalene derivatives, named cadalene and eudalene respectively, which he later proved by degradation and by synthesis to have the following structures.(1922)

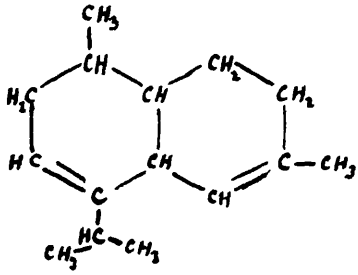


Cadalene

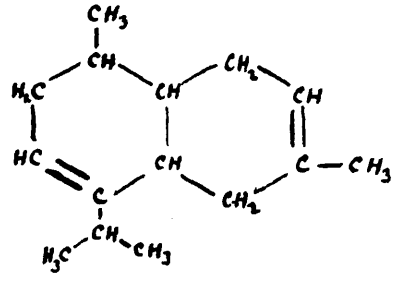


Eudalene

The bicyclic sesquiterpenes which yield cadalene are thus hexahydro-derivatives of this compound. Cadinene, for example, which can readily be converted to cadalene, has been shown to possess one or other , or possibly both of the following formulae (cf.p.)

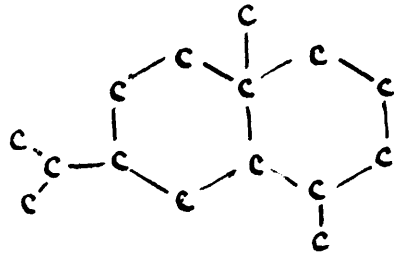


∝ -cadinene



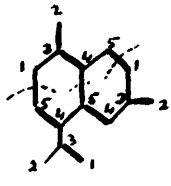
β -cadinene

In the case of eudalene, one carbon atom is removed during the dehydrogenation process, and in this case the parent sesquiterpene compounds (eudesmol, selinene, etc.) probably possess the following carbon skeleton



Eudesmol framework

Perhaps the most important result of this work is the demonstration it gives that the carbon skeleton of the sesquiterpenes may be derived by the aggregation of three isoprene residues end to end. Thus if we take three isoprene units, they may be put together in the form of a bicyclic system in the following three ways.



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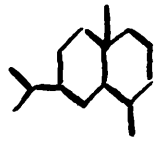

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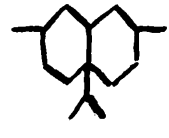
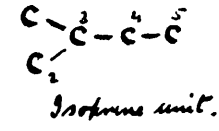


III



Isoprene unit.

Two of these systems represent the cadalene and eudalene framework respectively, but the third has not yet been derived from any natural sesquiterpene. This derivation of sesquiterpene skeletons by the aggregation of isoprene residues is a theoretical consideration of the first importance when considering the structural formulae of these compounds, and in fact it has been successful in predicting the structure of some sesquiterpenes.

The sesquiterpene alcohols may also in many cases be dehydrogenated with sulphur either directly e.g.

$$C_{15}H_{26}O + 3S = C_{15}H_{18} + H_2O + 3H_2S$$

$$C_{15}H_{24}O + 2S = C_{15}H_{18} + H_2O + 2H_2S$$

or by first converting the alcohol to the corresponding unsaturated hydrocarbon by elimination of the elements of water, and then treating the hydrocarbon with sulphur.

$$C_{15}H_{24} + 3S = C_{15}H_{18} + 3H_2S$$

Although there still remain many sesquiterpene compounds which yield no recognisable derivative even with the sulphur treatment, the classification of these complex bodies is now much more complete, and may be briefly summarised in the following table. The most important types which have not yet been dehydrogenated to a recognisable derivative are the cedrene, santalene, and caryophyllene series.

Classification of Sesquiterpene compounds.

Group	Sub-groups	Cadinene type	Eudesmol type
1.Tri-cyclic	a) Cedrene	----------	----------
	b) α-Santalene	----------	----------
	c) Copaen	$C_{15}H_{24}$ Copaen	----------
2.Bi-cyclic	a) Hydrogn. naphthalene compounds. "Heavy"class	$C_{15}H_{24}$ Cadinene $C_{15}H_{24}$ Calamene $C_{15}H_{26}O$ Cadinol $C_{15}H_{24}O$ Alc.from Java Citronella oil. $C_{15}H_{24}O$ Calamenol	$C_{15}H_{24}$ Selinene $C_{15}H_{26}O$ Eudesmol
	b) Terpene type "Light"class Caryophyllene, etc. $C_{15}H_{24}$	---------	----------
3.Mono-cyclic	(No sub-group)	$C_{15}H_{24}$ Zingiberene $C_{15}H_{24}$ Bisabolene $C_{15}H_{26}O$ Zingiberol	----------
4.Ali-phatic	(No sub-group)	$C_{15}H_{26}O$ Farnesol $C_{15}H_{26}O$ Nerolidol	----------

The compounds dealt with in the following pages belong chiefly to the bicyclic group, which includes by far the largest number of the natural sesquiterpenes. It may therefore be worth while to consider its sub-division in a little more detail.

Semmler, Becker (1913)[1] and Semmler, Tobias (1913)[2] showed that the group could be divided into a "heavy" and a "light" class, the former having a specific gravity of about .917 and the latter about .90 . The saturated hydrocarbons obtained from these compounds by catalytic reduction showed a similar variation in physical properties e.g.

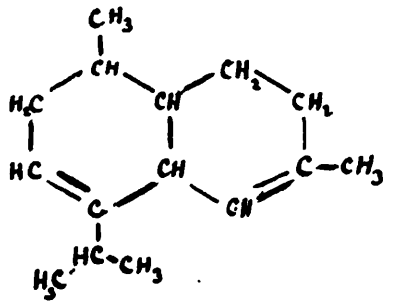
Heavy class $C_{15}H_{24} \longrightarrow C_{15}H_{28}$ d. 0.89. n_D 1.482

Light class $C_{15}H_{24} \longrightarrow C_{15}H_{28}$ d. 0.87. n_D 1.470

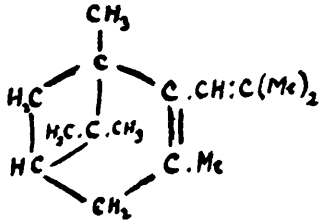
These regularities appeared to have a structural orign, and Semmler regarded the "heavy" class as partially hydrogenated naphthalene derivatives, a surmise which has now been substantiated by Ruzicka's work. Semmler regards the "light" bicyclic sesquiterpene class, on the other hand, as being derivatives of the bicyclic terpenes proper.

The two sesquiterpenes which are mostly widely distributed in nature are cadinene and caryophyllene. They are both bicyclic. Cadinene is typical of the "heavy" class a), a hydrogenated naphthalene derivative;

while caryophyllene is typical of the "light" class b), and may be regarded as a derivative of a bicyclic terpene. The exact structure of caryophyllene, however, has not been determined.



Bicyclic sesquiterpene
"Heavy" naphthalene type
(Cadinene)



Bicyclic sesquiterpene
"Light" terpene type
(Caryophyllene)

PART 1.

THE CADINENE SERIES.

Part 1.

THE CADINENE SERIES.

HISTORICAL.

Cadinene is the most widely distributed sesquiterpene in nature , and was the first member of the series to be definitely characterised. Its beautifully crystalline series of di-halogen hydride addition products have rendered its detection a matter of ease in a large number of ethereal oils. As early as 1840 it is described by Soubeiran and Capitaine[13] , who analysed the dihydrochloride. These authors make the interesting observation that while passing the vapour of the dihydrochloride over glowing lime there condensed in the cold part of the tube"a little of a crystalline material, having the appearance and smell of naphthalene". This experiment, however, has not been repeated, and the result is rather doubtful because in order to convert cadinene into naphthalene five carbon atoms would have to be eliminated from the former molecule. But these early observations are of interest as the recent work of Ruzicka has shown that cadinene is in fact a partially hydrogenated naphthalene derivative. It may be added that at this time (1840) cadinene dihydrochloride was referred to as " cubeb camphor " the name "cadinene" being introduced by Wallach[14] fifty years later when he found the sesquiterpene occuring in large

quantities in oil of cade (Oleum cadinum).

Schmidt ([15]) and Oglialoro (1876)[16] again isolated the dihydrochloride from oil of cubebs. The latter investigator first obtained the pure hydrocarbon from the dihydrochloride by heating it with water for a long time at 170°-180°.

Between 1887 and 1892 Wallach[17-19] published a series of investigations on cadinene. He describes many new sources of the oil, improved methods for obtaining it pure by regeneration from the dihydrochloride, various new additive compounds which characterise the sesquiterpene (dihydrobromide, dihydroiodide, nitrosate , nitrosochloride) etc. By oxidation with chromic acid he obtained a mixture of lower fatty acids, and with fuming nitric acid a yellow amorphous powder. By 1892 cadinene had been recognised as a constituent of oil of asafoetida, betel, cubebs, cade, camphor, coto-bark, galbanum, juniper, olebanum, paracoto bark, patchouli, and savin. Since then a large number of new sources of cadinene have been described.

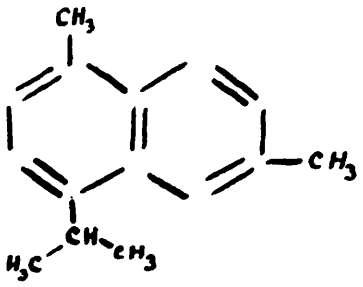
No work which gave any information as to the exact structure of cadinene was carried out until in 1914 Semmler and Stenzel[20] isolated the tricyclic sesquiterpene copaen from African copaiva balsam oil. This hydrocarbon is transformed by the action of hydrochloric acid into cadinene dihydrochloride. The structure of copaen is

therefore substantially similar to that of cadinene, the double bond in the former molecule occupying the same position as one of the double bonds in the cadinene molecule. Other evidence, mainly physical, indicated that the third ring of the copaen molecule takes the form of a valency bridge of the sabinene type, and breaks down with acid reagents. By oxidation with permanganate and ozone, copaen gave a ketonic acid (I) which upon further oxidation with bromine in caustic soda solution gave the dicarboxylic acid (II). It thus follows that one double bond in the cadinene molecule is adjacent to the iso-propyl group.

$C_{10}H_{16}\begin{cases} CO.C_3H_7 \\ COOH \end{cases}$ I

$C_{10}H_{16}\begin{cases} COOH \\ COOH \end{cases}$ II

In 1921[21] Ruzicka showed that by heating with powdered sulphur cadinene is converted into cadalene $C_{15}H_{18}$ a naphthalene derivative, and a later synthesis (1922)[22] showed that cadalene was a 1-6-dimethyl-4-isopropyl naphthalene



Cadalene

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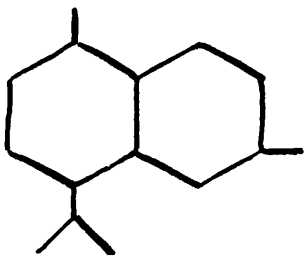
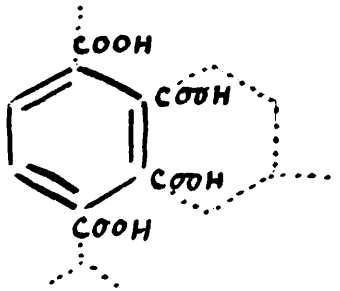
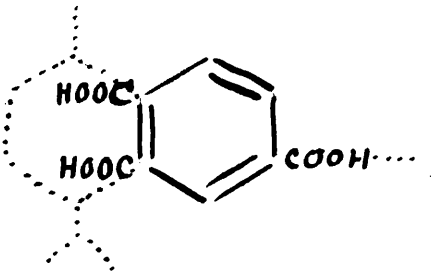


Cadinene framework

Cadinene therefore possesses the above carbon framework if no rearrangement has occured during the dehydrogenation process. The temperature of the reaction (200°- 250°) is rather high, and a molecular rearrangement is possible. Further confirmation, however, is afforded by an oxidation by Ruzicka and Stoll (1924). With manganese dioxide and sulphuric acid they obtained from cadinene two primary products, trimellitic and prehnitic acid, which have evidently been derived from the cadalene framework.

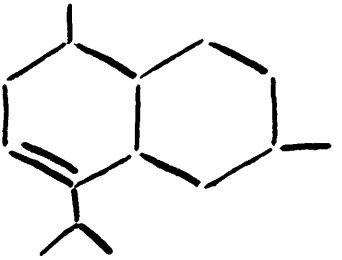


Prehnitic acid



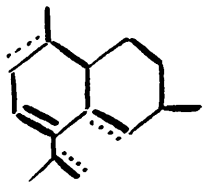
Trimellitic acid

Taking into account Semmler's copaen work, we may now represent what we know of cadinene by the following diagram:-

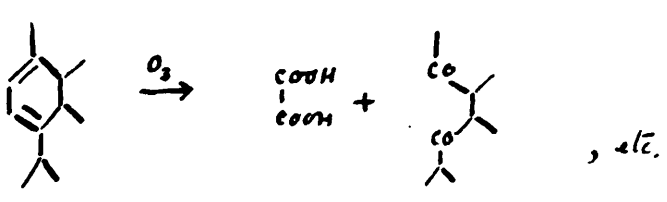


The problem which remains to be solved is the position of the second double bond in the molecule. Nothing is certainly known of this, although some positions

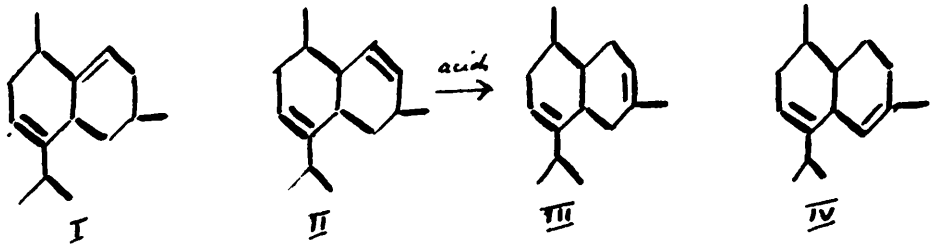
may be ruled out as being improbable. Thus, as cadinene forms no mono-halogen hydride addition product or dihydro reduction product, it is fairly certain that the molecule contains no conjugated double bond system. This consideration rules out the following positions for the second double bond(shown thus ····)



Further, Ruzicka and Stoll (1924)[23] obtained an ozone product from cadinene, which was not very definite, but which they appear to have obtained sufficiently pure as a dicarboxylic diethyl ester to state its empirical formula as either $C_{19}H_{30}O_5$ or $C_{19}H_{32}O_6$. This result shows that all the carbon atoms in the cadinene ozone product have remained intact, and therefore we may state that all the formulae having two double bonds in the same ring are improbable, because if that were the case part of the molecule would be split off in the ozone process.eg.

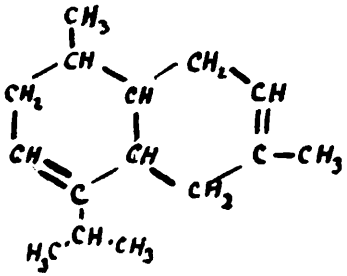


These considerations leave us with four possible formulae for cadinene:-

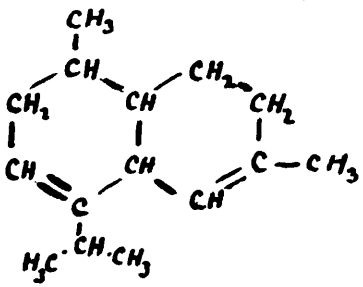


I II III IV

Ruzicka thinks that (I) and (II) are not probable as they would tend to be unstable, especially towards acids. His conclusion therefore is that cadinene may be represented by one or both of the following formulae:-



β -cadinene



α -cadinene

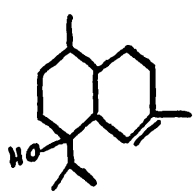
ISOCADINENE

In oil of cade and other ethereal oils it has long been known that there occurs associated with cadinene another sesquiterpene of closely similar physical properties, but which only yields liquid adddtion products with the halogen acids. It has been isolated by Troger and Feld mann (1898)[24] by Lepeschkin (1908),[25] and by Henderson and Robertson (1924).[26] It has not, however, been characterised by any crystalline

derivative. The last authors also found that cadinene itself on heating with acetic acid in a sealed tube is converted into an isomeric hydrocarbon named iso-cadinene which again only gives a liquid dihydrochloride, and which appears to be identical in all its properties with the natural sesquiterpenes described above.

CADINOL

Wallach (1887)[17] found that the higher boiling fractions of galbanum oil yielded cadinene dihydrochloride on treatment with hydrochloric acid, and later Semmler and Jonas (1914)[27] showed that these fractions contained in addition to cadinene a bicyclic sesquiterpene alcohol, cadinol, $C_{15}H_{26}O$, which yielded cadinene dihydrochloride on treatment with hydrochloric acid , and which must, therefore, be closely related to cadinene. A liquid acetate was the only derivative which could be prepared from cadinol, which was therefore supposed to be tertiary. Ruzicka and Stoll (1924)[28] as a sequel to their work described above, point out that cadinol may have three formulae:-



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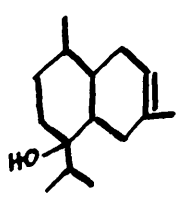

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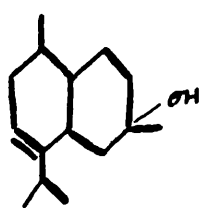


γ

But these results must be taken with caution, as the ozone products obtained are very indefinite, and further it was not possible to make a crystalline derivative from cadinol and so obtain it in a pure state.

The following work describes

(1) Certain oxidations of cadinene.

(2) A proof of the relation of the iso-cadinene hydrocarbons to cadinene.

(3) The discovery and characterisation of a new bicyclic sesquiterpene alcohol related to cadinene.

THEORETICAL.

Oxidations.-From the foregoing discussion it will be seen that although the carbon framework of cadinene has been exactly determined, yet considerable doubt remains as to the position of the double bonds in the molecule. The configuration currently assigned has been arrived at by a process of elimination rather than direct proof. In order to establish the formula for cadinene it is most desirable in the first instance to obtain if possible some direct oxidation products, containing all, or nearly all, the molecule intact. Although previous efforts in this direction have met with no success, it seemed desirable to examine the reaction of cadinene with certain oxidising agents, such as chromyl chloride and hydrogen peroxide, which have been found to yield such good results with the ordinary terpenes. (cf. Henderson and others, 1903-1922.) [29-31] The following work was therefore undertaken with this object in view.

The cadinene used in the following experiments was prepared by treating the appropriate fraction of oil of cade or oil of cubebs with dry hydrogen chloride in glacial acetic acid solution. The dihydrochloride was then isolated and purified, and pure cadinene regenerated by treatment with sodium acetate in hot glacial acetic acid, or with an alcoholic solution of sodium ethoxide.(cf.EXP.)

Several oxidations with hydrogen peroxide in acetic acid solution were carried out. The results, however, were not satisfactory. The product, isolated by the usual methods, consisted in all cases of a non-crystalline resinous material, which could only be purified with the greatest difficulty. The resin was hard and brittle at ordinary temperarure, became liquid at 100°, and could be distilled at 170°, with some decomposition, in the high vacuum afforded by the mercury pump (about 0.5-1mm.). The product, prepared and purified in several different ways, gave a fairly constant analysis, agreeing approximately with the formula $(C_{15}H_{24}O_4)_x$. The oxidation appears to have been accompanied with polymerisation of the cadinene molecule.

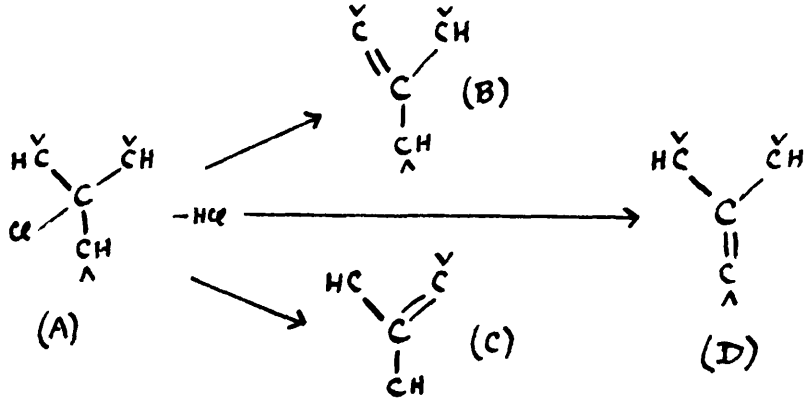
It was found that in dilute solution cadinene reacts readily with chromyl chloride to form an additive compound, whose composition agrees approximately with the formula $C_{15}H_{24}3CrO_2Cl_2$. This compound is of a whitish brown colour when dry. It reacts comparatively slowly with moist air, and is completely decomposed by water. When decomposed with water in the usual manner, in addition to small quantities of an acid product, a ten per cent yield of a steam volatile neutral product was obtained, which did not give a crystalline semicarbazone even after prolonged treatment. Owing to the relatively small yield of workable product, and the difficulty involved in the

preparation of a sufficient quantity of cadinene, this investigation was not continued.

Wallach (1887) found that by oxidation with chromic acid cadinene gives a mixture of lower fatty acids. The present experiments, however, showed that while potassium dichromate and sulphuric acid mixture gave products which were entirely acid, yet upon careful oxidation with chromic anhydride in glacial acetic acid solution, in addition to some resinous acids, a neutral product consisting of an unsaturated oil of a light yellow colour was obtained, b.p.180-196°/12mm., whose composition agrees with the formula $C_{15}H_{24}O_2$. No definite evidence of the presence of ketonic or hydroxyl groups could be obtained as the substance did not react with semicarbazide mixture, p.nitro-benzoyl chloride, or phenyl iso-cyanate under the usual conditions. When treated with metallic sodium the oil polymerised to form a semi-solid jelly. This substance agrees in its properties with the hydroxy-ketone described by Ruzicka and Stoll (1924). These substances, however, are too indefinite to be of use in a discussion of structure.

The oxidation products above described have in all cases been difficult to isolate and purify, which is in general the experience of other investigators in this direction. This may be due to the fact that, in dealing with a hydrocarbon which is regenerated from a dihydrochloride, the presence of a complex mixture of closely related

isomers is possible. The chlorine atoms being attached to tertiary carbon atoms, the elimination of hydrogen chloride from the molecule may take place in a variety of ways.



A structure such as (A), for example, upon elimination of hydrogen chloride can give rise to (B), (C), and (D), and it is evident that from a dihydrochloride nine such isomers are theoretically possible. In the case of complex bodies such as cadinene some of these theoretically possible isomers may be actually present, whose closely similar physical properties would prevent their detection by distillation methods. There would thus be little chance of obtaining a uniform oxidation product from such a complex starting material.

The failure to obtain a tetra-halogen addition product in a uniform state from compounds such as cadinene is a fact which lends support to the above hypothesis.

Iso-cadinene.- The sesquiterpene from cade oil (Henderson and Robertson, 1924) was further examined. In one attempt to obtain a crystalline derivative from it, the liquid hydrochloride was treated with silver acetate in glacial acetic acid solution. Hydrolysis of the product, however, yielded no solid hydroxyl compound. By dehydrogenation with sulphur, the cade oil sesquiterpene yielded cadalene, which was identified by its picrate, m.p.114°.

A quantity of iso-cadinene was prepared by heating cadinene under pressure with acetic acid. This substance, in a comparatively pure state, was found also to dehydrogenate readily with sulphur to give cadalene. The yield of cadalene in this case was equal to the yield obtained from pure cadinene by the same method.

It is therefore evident that iso-cadinene contains the same carbon skeleton as cadinene, and can only differ from it in the position of the double bonds in the molecule.

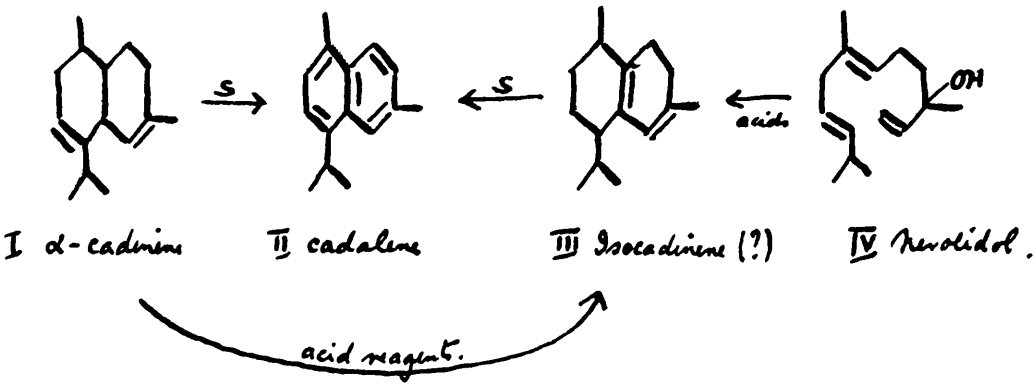
In their recent synthesis of bisabolene from nerolidol by acid reagents, Ruzicka and Capato (1925) have shown that prolonged heating with acids closes two rings of the nerolidol structure, and the product is a hexahydrocadalene, which most probably has the constitution (III). This substance had

b.p.125-126°/12mm., d.0.916, n_D 1.509

and only yielded a liquid hydrochloride. Now the constants for iso-cadinene are

b.p.124-126°/11mm., $d_{4^\circ}^{20^\circ}$ 0.915 $n_D^{20^\circ}$ 1.515.

The close similarity of these compounds is evident. As they are both produced by the action of acids on the hexahydrocadalene framework it is probable that iso-cadinene is indeed identical with this synthetic product of Ruzicka's, which in that case will represent the end product to which the hexahydrocadalenes are transformed by the action of acid reagents. The chief difficulty which impedes the further progress of this work is the want of any characterising derivative for iso-cadinene. All that has been definitely established so far is that iso-cadinene is a hexahydrocadalene.



Isolation of new bicyclic sesquiterpene alcohol.- It is a remarkable fact that although cadinene is so widely distributed in nature, the alcohol cadinol has hitherto been discovered in only one plant source, viz. galbanum oil. While preparing cadinene dihydrochloride for the foregoing experiments from the sesquiterpene fraction of oil of cubebs, it was observed that a good yield of the dihydrochloride was obtained from the higher boiling portions. Repeated distillation of the oil under diminished pressure led to the isolation of a number of fractions, an examination of whose physical properties indicated that there were at least two compounds present. A graph of the rotatory power of the various fractions is given on the following page, and it clearly shows the presence of at least two compounds. Further work led to the isolation of a fraction, b.p.148-160°/10mm., of a dark green colour which appeared to have the properties of cadinol. After hydrolysis and redistillation most of this portion was obtained as an unsaturated alcohol , $C_{15}H_{25}(OH)$, which had

b.p.153-155°/10mm., $d_{4^\circ}^{16^\circ}$ 0.9727, $n_D^{16^\circ}$ 1.508, $[\alpha]_{5461}^{15^\circ}$ -54°

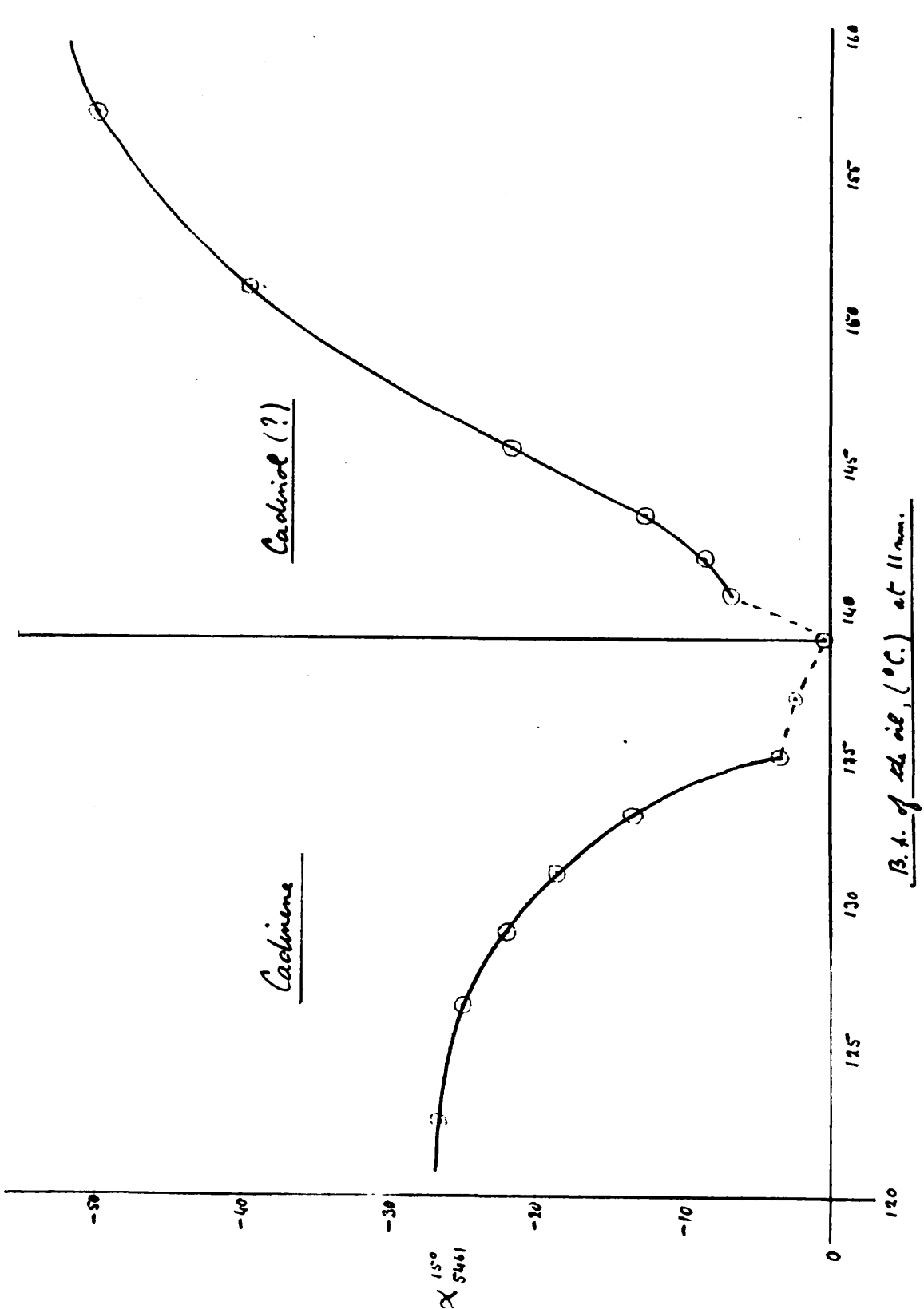
molecular refractivity = 68.0

and which gave a good yield of cadinene dihydrochloride when treated with dry hydrogen chloride. Semmler's cadinol from galbanum oil had

b.p.155-165°/12mm., d_{20° 0.9720, n_D 1.50702, α_D +22°

molecular refractivity = 67.97.

Graph showing variation in rotatory power with b.p.



Molecular refractivity calculated for a bicyclic sesquiterpene alcohol = 68.12. Hence the new alcohol is closely similar in all its properties to the galbanum cadinol, except that it is laevo- rotatory.

Hitherto no alcohol of the bicyclic sesquiterpene series has been known to yield a crystalline ester. These alcohols are usually tertiary, and readily part with the elements of water to form the corresponding doubly unsaturated hydrocarbon, $C_{15}H_{24}/\overline{2}$. Some of them give a liquid acetate, which, however, is of little value for characterising the alcohol.

The present experiments showed that when the above alcohol from oil of cubebs was treated with phenyl iso-cyanate, employing a somewhat modified method, a crystalline phenylurethane derivative was obtained, $C_{15}H_{25}O.CO.NH.C_6H_5$. This compound is dextro-rotatory. It is unsaturated, and unites with bromine to form an unstable dibromide, $C_{22}H_{31}Br_2O_2N$.

It was shown (Henderson and Robertson, 1924) that cadinene dihydrochloride reacts with silver acetate to give a mixture of acetates, from which, after hydrolysis, they isolated a glycol, $C_{15}H_{26}(OH)_2$ and an unsaturated alcohol $C_{15}H_{25}(OH)$. A quantity of this synthetic alcohol was now prepared by their method. It did not, however, react with phenyl iso-cyanate under the same conditions as described above. Hence the synthetic alcohol appears to be isomeric with the alcohol obtained from oil of cubebs.

It is possible that this alcohol from oil of cubebs may be structurally different from cadinene dihydrochloride and only revert to that type on treatment with hydrochloric acid, just as many compounds in the terpene series, such as pinene and cineole can give dipentene dihydrochloride when treated with hydrochloric acid. Some evidence that certain naturally occuring sesquiterpenes which yield cadinene dihydrochloride differ from the regenerated hydrocarbon has been brought forward by Semmler and Jonas (1914)[33] and also by Deussen (1900)[34]. This evidence is based largely upon physical properties.

EXPERIMENTAL.

Preparation of cadinene.- Oil of cubebs was fractionally distilled under reduced pressure. The sesquiterpene fraction, b.p. 120-140°/10mm., was treated with dry hydrogen chloride in glacial acetic acid solution. After standing for two days at 0°, the cadinene dihydrochloride which formed was collected and purified. M.p.118°. In some of the preparations anhydrous ether was used as a solvent instead of acetic acid, but it was generally found that the yield was not so good in ethereal solution.

Cadinene dihydrochloride (120 g.) was dissolved in glacial acetic acid (500 g.) at 90°-100°, and anhydrous sodium acetate (120 g.) was gradually added. After a short time sodium chloride began to separate. The reaction was complete in about four hours, when the mixture was cooled, excess of water added, and the cadinene extracted with light petroleum ether. It was finally purified by distillation under reduced pressure, and had

b.p.130-134°/10mm., $d_{4}^{20°}$ 0.9189, $n_{D}^{20°}$ 1.5079, $[\alpha]_{5461}^{18°}$ -125°.

It was also found that when cadinene dihydrochloride was refluxed for several hours with an alcoholic solution of sodium ethoxide, and the product worked up as before, an equally pure specimen of cadinene was obtained.

Oxidation of cadinene with hydrogen peroxide.- 50 g. of cadinene (1 mol.) were dissolved in 200 g. of glacial acetic

acid and 55 g. of thirty per cent hydrogen peroxide (2 mols.) added, two layers forming. The mixture was maintained at 50° for thirty hours, when the reaction appeared to be complete The acetic acid was neutralised with sodium carbonate, water being added in sufficent quantity to keep the sodium acetate in solution. The product was repeatedly extracted with ether. On removing the ether from the dried extracts, a hard yellow resinous substance remained which could not be obtained crystalline from any solvent. It could not be ~~obtained~~ purified by ordinary vacuum distillation, but with the aid of the mercury pump it distilled with some decomposition.

b.p. 170-180°/0.5mm.

The product was still resinous and yielded no derivative by the usual methods.

ANALYSIS

.2617 g. gave .5540 g. CO_2, .1842 g. H_2O.

Found - - - C = 69.7, H = 9.4 per cent

$(C_{15}H_{24}O_4)_x$ requires C = 67.2, H = 9.0 " "

In another experiment, the product from the oxidation was treated with methyl alcoholic potash to remove any esters which might be present. After further purification and distillation, the final product consisted of a bright yellow resin, which proved to be the same as that described above.

ANALYSIS

.1573 g. gave .3917 g. CO_2, .1416 g. H_2O
.1255 g. gave .3179 g. CO_2, .1136 g. H_2O

Found - - - - C = 67.9, H = 10.0 per cent
C = 69.0, H = 10.1 " "

$(C_{15}H_{24}O_4)_x$ requires - C = 67.2, H = 9.0 per cent

These analysis, on different portions of the product, show that it was nearly homogeneous.

Action of chromyl chloride on cadinene.- 200 cc. of carbon tetrachloride were placed in a large flask and cooled with ice-water. A ten per cent solution of cadinene in carbon tetrachloride and a ten per cent solution of chromyl chloride in the same solvent were added to this alternately in small quantities at a time, with stirring after each addition. In this way the concentration of the reacting substances was kept very low. A brown compound separated immediately, the amount of chromyl chloride required to complete the reaction being a little less than that required by the formula $C_{15}H_{24}.3CrO_2Cl_2$ for the addition product. The additive compound was collected and purified by washing with carbon tetrachloride. When dry it was a whitish brown colour, and reacted slowly with moist air.

The additive compound was decomposed by gradual addition to a mixture of ice and water. The organic products were extracted with ether and warmed with sodium carbonate solution. In this way, from the sodium salts,

a small quantity of a rather sticky acid was obtained, which could not be crystallized. The neutral products were steam distilled when an oil was obtained in about ten per cent yield, the residue consisting of resinous materials. This oil was treated with semicarbazide mixture in the usual manner, but even after prolonged treatment no crystalline semicarbazone could be obtained. A fuller investigation was not made owing to the large quantity of cadinene which would have been required.

Oxidation of cadinene with chromic anhydride.- The reaction was conducted as follows. Chromic anhydride (70 *g.*) dissolved in a little water and diluted with acetic acid was slowly added with constant stirring to cadinene (50 *g.*) in glacial acetic acid (250 *g.*). The operation lasted one hour, and the temperature was maintained below 50° by occasional cooling. Finally the mixture was heated on the water bath till green, water added, the products extracted with ether and dried over anhydrous sodium sulphate. After removing the ether they were neutralised with sodium carbonate. The neutral products were again extracted with ether and dried. As they were only slowly volatile in steam, they were purified by fractional distillation in a high vacuum by means of the mercury pump. Three fractions were obtained.

(a) b.p. 85 -110°/0.5mm.

(b) b.p. 110-140°/0.5mm.

(c) b.p. 140-150°/0.5mm.

The fraction (a) proved to consist largely of unchanged cadinene, as it gave the dihydrochloride, m.p. 118°, on treatment with dry hydrogen chloride in glacial acetic acid solution.

ANALYSIS

.1493 g. gave .4658 g. CO_2, .1547 g. H_2O.

Found - - - C = 85.1, H = 11.5 per cent

Fractions (b) and (c) were found to contain a small amount of resin acid, which was removed by warming with caustic soda solution. Redistillation of the resulting product gave a light yellow oil

b.p. 180-196°/12mm., $n_D^{6.5}$ 1.5095

ANALYSIS

.1367 g. gave .3839 g. CO_2, .1251 g. H_2O.
.1556 g. " .4340g. ", .1338 g. H_2O.

Found - - - - C = 76.6, H = 10.2 per cent
C = 76.1, H = 9.6 " "

$C_{15}H_{24}O_2$ requires - C = 76.3, H = 10.2 " "

This oil was unsaturated towards bromine and alkaline permanganate. It did not give a semicarbazone, neither did it react with p.nitro-benzoyl chloride in pyridine solution or with phenyl iso-cyanate. Treatment with hydrogen chlor-

-ide gave a black tarry product which could not be purified In the hope of obtaining evidence of the presence of hydroxyl groups, finely divided metallic sodium was added to the oil. A semi-solid jelly was produced, but no hydrogen was liberated. Many other experiments on this substance were attempted, but no definite results were obtained.

The acid products of the oxidation were obtained by acidifying the sodium salts and extracting the resulting oil with ether. After drying, the ether and acetic acid present were completely removed under reduced pressure, when a resinous acid was obtained as principal product, which gave silver and sodium salts which were not crystalline

ANALYSIS of the acid

.1338 g. gave .2892 g. CO_2, .1019 g. H_2O
.1819 g. " .3950 g. " , .1382 g. "

Found - - C = 58.9, H = 8.5 per cent.
C = 59.2, H = 8.4 " "

.2742 g. silver salt gave .0971 g. silver
.2247 g. " " " .0796 g. "

Found silver = 35.41 per cent
" = 35.42 " " .

Oxidation of cadinene with potassium dichromate and sulphuric acid mixture.- Cadinene (10 g.) in acetic acid (50 cc.) was treated with potassium dichromate (20 g.) and sulphuric acid (14 cc.) in a mixture of water and acetic acid. The temperature was maintained about 50°, and the

reaction completed by warming on the water bath till green. The products were worked up as before. In addition to a little unattacked cadinene, there resulted only an acid product, which on purification gave silver and sodium salts and which from its analysis appears to be identical with the resin acid described above.

ANALYSIS

.1377 g.gave .3017 g. CO_2, .1073 g. H_2O .

Found - - C = 59.7, H = 8.7 per cent.

.2482 g. silver salt gave .0872 g. silver
.2431 g. " " " .0850 g. "

Found silver = 35.1 per cent
" = 35.0 " " .

ISO-CADINENE.

Preparation of iso-cadinene.- Cadinene (10 g.) was mixed with glacial acetic acid (30 g.) and heated to 200°-220° for thirty hours in sealed tubes. Two layers formed. After neutralising the acetic acid with sodium carbonate, the oil was extracted with ether, dried, and distilled under reduced pressure.

b.p. 121 -124°/9mm., $d_{4^\circ}^{16^\circ}$ 0.915

It did not form a stable hydrochloride.

Dehydrogenation with sulphur.- Iso-cadinene (2.4 g.) was mixed with finely powdered sulphur (1.2 g.) and heated on the oil bath to 200°. A considerable evolution of hydrogen sulphide took place, and the temperature was gradually raised to 250°. After one and a half hours the reaction was complete. The product was distilled under diminished pressure when a yellow oil was obtained, b.p. 130 -150°/9mm. This was redistilled over sodium and yielded a colourless liquid, b.p. 140 -150°/9mm. The yield was fully fifty per cent. A portion was treated with an alcoholic solution of picric acid, and a solid mass of red crystals was immediately formed. They were drained and purified by crystallisation from alcohol. M.p. 114°.

Some cadalene was prepared from pure cadinene by the same method. The yield was the same. Its picrate also melted at 114°. Mixed m.p. of the two picrates = 114°.

Sesquiterpene from oil of cade.- This compound, purified as described by Henderson and Robertson (1924) had

b.p. 124-128°/12mm., $d_{4^\circ}^{20^\circ}$ 0.918 $n_D^{20^\circ}$ 1.516.

It yielded no crystalline hydrochloride. A portion was dehydrogenated with sulphur as described above, when a good yield of cadalene was obtained, giving the picrate with m.p. and mixed m.p. 114°.

ALCOHOL FROM OIL OF CUBEBS.

Isolation of an l-bicyclic sesquiterpene alcohol.- Oil of cubebs was fractionally distilled under reduced pressure. After a large number of distillations a fraction, b.p. 148-160°/10mm., was finally isolated, consisting of a bluish green viscous liquid. This liquid (120 g.) was hydrolysed by warming with dilute methyl alcoholic potash for half an hour, the alcohol distilled off, water added, and the product extracted with ether and dried over anhydrous sodium sulphate. After removing the ether the product was distilled under reduced pressure. The larger part (80 g.) consisted of a bluish green liquid which had

b.p.153 -155°/10mm., $d_{4^\circ}^{16^\circ}$ 0.9727, $n_D^{16^\circ}$ 1.508, $[\alpha]_{5461}^{15^\circ}$ -54°,

molecular refractivity = $\frac{n^2 - 1}{n^2 + 2} \cdot \frac{M}{d}$ = 68.00

mol. refr. calculated for $C_{15}H_{26}O$ III = 68.12

ANALYSIS

.2208 g. gave .5987 g. CO_2, .2092 g. H_2O.

Found - - - - C = 81.3, H = 11.6 per cent

$C_{15}H_{25}(OH)$ requires - C = 81.1, H = 11.7 " " .

The alcohol is unsaturated, and gave a thirty per cent yield of cadinene dihydrochloride, (m.p. 118°, $[\alpha]_{5461}^{16^\circ}$ -43.7° in 2.380 per cent chloroform solution) when treated with dry hydrogen chloride in glacial acetic acid solution.

Preparation of phenyl-urethane derivative.- The alcohol (20 gm) and phenyl iso-cyanate (10 g.) were heated together for fifteen hours at 80 -100°. On cooling, diphenylurea, m,p. 238°, crystallised out, leaving a dark coloured oil. This oil was freed from the diphenylurea by repeated extraction with anhydrous ether in which diphenylurea is nearly insoluble. After removing the ether the oil was taken up in alcohol, and water added to the point of precipitation. On standing some time at 0°, the oil phenylurethane derivative crystallised out in well defined needles. It was purified by repeated extraction with anhydrous ether, and recrystallisation from alcohol, in which it is moderately soluble. M,p. 186°.

ANALYSIS

.1081 g. gave .3053 g. CO_2, .0916 g. H_2O .

.1994 g. gave 7.75 cc. N at 23°, 760mm.

Found - - - C = 77.0, H = 9.4, N = 4.5 per cent

$C_{21}H_{31}O_2N$ requires - C = 77.4, H = 9.1, N = 4.1 " " .

The compound is dextro-rotatory,

$[\alpha]^{19°}_{5461}$ = +58.9° in 5 per cent chloroform solution.

The yield was about five per cent, but it was found that this could be increased by the following method. After no more crystals separated from the alcoholic solution on long standing , the liquid was steam distilled. The steam

distillate consisted of hydrocarbons and unattacked alcohol, and from the residue a further quantity of the phenyl-urethane could be crystallised.

The phenyl-urethane derivative is unsaturated. An alcoholic solution was treated with an excess of bromine and a solid compound separated on the addition of a little water. It proved to be rather unstable, decomposing at 76°-80°, and could not be satisfactorily purified, owing to the small quantity available. The analysis indicates that it is a dibromide.

ANALYSIS

.1676 g. gave .1502 g. AgBr

Found - - - - Br = 38.1 per cent

$C_{21}H_{31}Br_2O_2N$ requires - Br = 32. " " .

Preparation of synthetic cadinol.- By slightly modifying the method described by Henderson and Robertson (1924) a sixteen per cent yield of the alcohol

b.p. 153°- 160°/10mm., $d_4^{17°}$ 0.9777, $n_D^{14°}$ 1.5053

molecular refractivity = 67.36

was obtained. The silver acetate was added gradually over a period of three hours to a solution of 50 g. of cadinene dihydrochloride in 600 cc. glacial acetic acid at 50-55° .

Part of this large excess of acetic acid was removed by distillation under reduced pressure, and the remainder was neutralised with sodium carbonate. The steam distillation was continued for five hours. The remainder of the operation was carried out as described (loc.cit.)

This alcohol did not give a phenyl-urethane derivative under the conditions described above.

PART 2.

THE CHEMISTRY OF THE CARYOPHYLLENE SERIES.

Part a.

THE CHEMISTRY OF THE CARYOPHYLLENE SERIES.

HISTORICAL.

Caryophyllene was first definitely characterized by Wallach[35] (1911) who found that upon hydration with a mixture of sulphuric and acetic acids a crystalline hydrate known as caryophyllene alcohol is formed, which is quite characteristic of this sesquiterpene. At this time no crystalline addition products of caryophyllene with the halogen acids were known, although Wallach[35, 6] showed that the alcohol gave a series of halogen derivatives and esters. The formation of the crystalline hydrate proved a ready means for the detection of caryophyllene in various ethereal oils and it was shortly afterwards shown to occur in oil of cloves and clove stems, copaiba balsam oil, oil of Canella alba, etc. These results were confirmed by the discovery that caryophyllene yielded a crystalline nitrosochloride and nitrosate.[36,37] As far as our present knowledge goes it seems probable that with the exception of cadinene, caryophyllene is the most widespread representative of the naturally occuring sesquiterpenes. (cf. Ruzicka[38]) In view of this it is interesting to notice that caryophyllene alcohol has not yet been found to occur in nature, a fact which seems to point to a structural difference between the alcohol and the hydrocarbon.

Later work by Deussen [39-42] has shown that caryophyllene consists of a mixture of two closely related isomers; α-caryophyllene which is optically inactive, and gives liquid addition products with the halogen acids; and β-caryophyllene which is optically active and gives a characteristic dihydrochloride. There is also some evidence of a third isomer known as γ-caryophyllene which can be formed indirectly from the nitrosite of β-caryophyllene. This work is supported by a very complicated series of relations between the nitrosites, nitrosates, and nitroso-chlorides of these hydrocarbons; but as these experiments do not directly concern this work, they are only mentioned here. (cf. [39-42])

The following work is concerned with the chemistry of β-caryophyllene, which can be obtained in a practically pure state by fractional distillation of oil of cloves. This hydrocarbon gives a good yield of caryophyllene alcohol and also of the dihydrochloride.

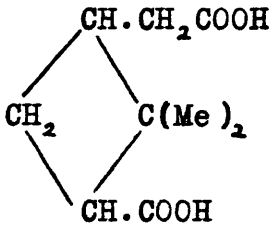
The evidence afforded by the molecular refractivity measurements leaves little doubt that β-caryophyllene contains two double bonds. This result is confirmed by the isolation of a tetrahydro-derivative prepared by catalytic hydrogenation (Semmler and Mayer, 1912 [43]) and by the preparation of crystalline additive products from the nitrosite $C_{15}H_{14}N_2O_3$ with hydrogen chloride and hydrogen bromide.[42]

Hence it may be regarded as certain that β -caryophyllene belongs to the bicyclic series of sesquiterpenes. But since it has been shown by Ruzicka [44] and by Deussen [ ] that no naphthalene or benzenoid derivative can be prepared from caryophyllene by the sulphur method, it cannot be assigned to either of the known cadinene or eudesmol types. (cf. p.). It must, therefore, possess a new and more complicated type of structure than that met with in the case of cadinene and its derivatives.

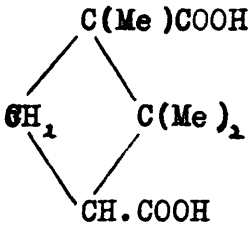
Little is known with certainty regarding the constitution of caryophyllene. By the action of ozone Semmler and Mayer obtained a variety of products from the hydrocarbon, the most important of which were a keto-acid $C_{11}H_{18}O_3$, a diketo-acid $C_{14}H_{22}O_4$, a ketone $C_{10}H_{16}O$, and a diketone $C_{12}H_{20}O_2$. Other products were obtained which were not so definitely characterized. Except the ketone $C_{10}H_{16}O$, all these products upon further oxidation yielded a stable end product consisting of a dicarboxylic acid $C_9H_{14}O_4$, which could not be oxidised further.

This compound, called caryophyllenic acid, is isomeric with pinic acid, but can give an anhydride $C_9H_{12}O_3$. From its general properties and its resemblence to pinic acid Semmler considers caryophyllenic acid to be cis-1-3-dicarboxy-2-2-3-trimethylcyclobutane. Its stability indicates a cyclobutane ring, and the formation of dimethyl-

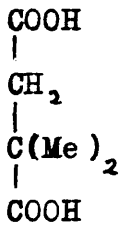
-succinic acid in the further oxidation of the ozonide products side by side with caryophyllenic acid affords confirmation of the existance of a $>C(CH_3)_2$ group in the latter compound.



Pinic acid.

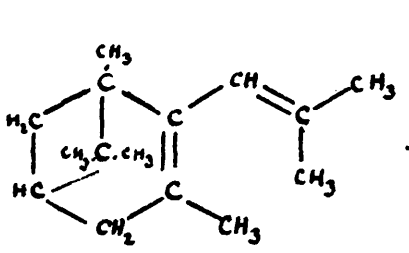


Caryophyllenic acid

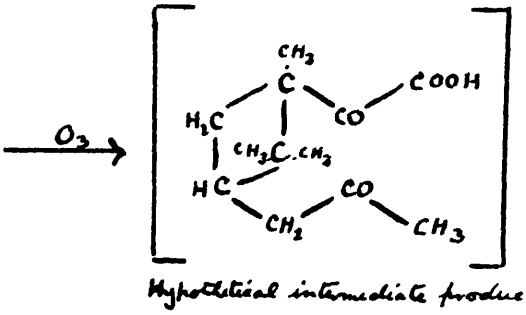


Dimethyl succinic acid

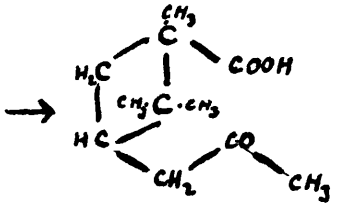
The formula advanced for caryophyllenic acid is thus tentative. Assuming the above structure to be correct the production of the keto-acid, $C_{11}H_{18}O_3$ from caryophyllene may be explained most simply by the following scheme due to Semmler.-



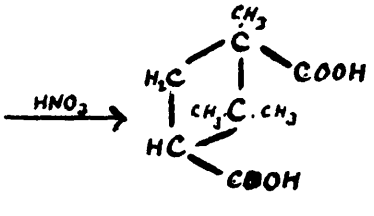
Dihydrocaryophyllene



Hypothetical intermediate product

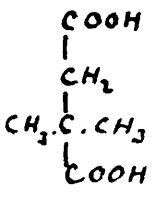


$C_{11}H_{18}O_3$



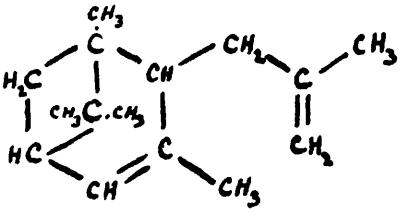
Caryophyllenic acid

+

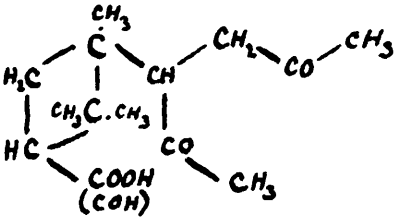


Dimethyl succinic acid.

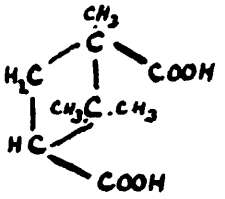
Further oxidation of the di-keto acid, $C_{14}H_{22}O_4$, results in the production of succinic acid and anhydride as well as caryophyllenic acid. Semmlers view of this reaction is as follows :—



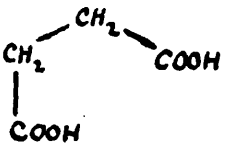
Lim. caryophyllene



$C_{14}H_{22}O_4$ diketo-acid
(or diketo-aldehyde)



Caryophyllenic acid



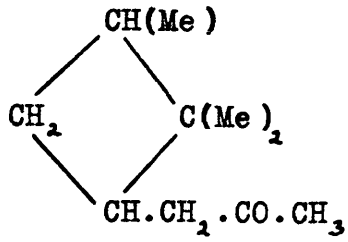
Succinic acid

The ketone $C_{10}H_{18}O$, another ozonide product, underwent further oxidation in alkaline bromine solution as follows:-

$$C_{10}H_{18}O \xrightarrow[KOH]{Br} CBr_4 + C_9H_{16}O_2$$

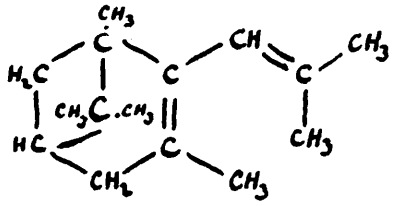
and therefore is of the type $R.CO.CH_3$. It was further shown that this ketone can lose two carbon atoms to give a cyclic monobasic acid $C_8H_{14}O_2$, and therefore appears to contain the caryophyllenic acid skeleton . Thus the

ketone probably has the following structure :-

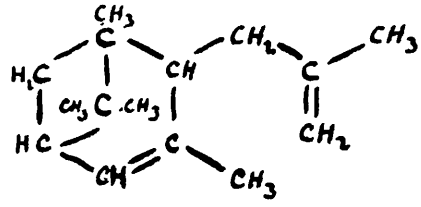


The methyl ketone.

The fact that none of the above oxidation products are crystalline and that only a few crystalline derivatives have been prepared from them renders the question of their purity open to doubt. The following formulae for caryophyllene which Semmler deduces from these reactions cannot, therefore, in any sense be regarded as final



Terp. caryophyllene



Lim. caryophyllene

It may be noted that the names Terpinolene and Limonene used by Semmler to denote the two isomers which he considers constitute active caryophyllene are derived by analogy from the terpene series. These formulae may be taken to represent our present knowledge of the reactions of caryophyllene, and they shall therefore be used as a basis in the following discussion which concerns the structure of

Wallach's caryophyllene alcohol, and the synthesis of certain other hydroxyl derivatives of caryophyllene.

There is some evidence which indicates that caryophyllene alcohol and its derivatives possess a different molecular configuration from that assigned to caryophyllene. Wallach[4] states that the alcohol is saturated, and found that dehydration of the alcohol yielded a hydrocarbon, $C_{15}H_{24}$, called clovene, which differed from caryophyllene, and whose physical properties indicated that it contained only one ethylene linkage. This hydrocarbon, however, has not been definitely characterized. Later Semmler[5] took up this question and found that caryophyllene alcohol was tertiary as it yielded neither a ketone nor an aldehyde by oxidation with bichromate and sulphuric acid. By reduction with zinc dust under pressure he obtained a saturated hydrocarbon $C_{15}H_{26}$ which contained no double bonds, but he states that there is no direct evidence to show how many double bonds caryophyllene alcohol contains. The fact that this alcohol is a solid melting at 96° renders impracticable the usual measurements for determination of molecular refractivity.

The following work was carried out in order to obtain more information regarding the properties of caryophyllene alcohol, and in particular to ascertain its relation to parent hydrocarbon.

THEORETICAL.

Caryophyllene alcohol was prepared by a slight modification of Wallach's hydration method which rendered the process suitable for dealing with large quantities at a time. The alcohol has the empirical formula $C_{15}H_{25}(OH)$. In a pure state, it was found to be remarkably stable in certain respects. Thus, after heating with hydrogen peroxide for fifty-two hours, practically the whole of the alcohol was recovered unchanged. On treatment with permanganate the alcohol was again recovered unchanged. Towards bromine in chloroform solution, it behaved as a fully saturated substance.

All known bicyclic sesquiterpene alcohols of the formula $C_{15}H_{25}(OH)$ are unsaturated, uniting additively with bromine and being readily oxidised. It is evident that caryophyllene alcohol does not belong to this class and therefore cannot be regarded as a direct hydrate of the hydrocarbon as previously supposed. Apparently the hydrating agents have induced ring closure with the formation of a new tricyclic structure. Confirmation of this view is found in the fact that the alcohol can be formed through the agency of formic acid, which is a well known means of effecting ring closure in the sesquiterpenes. (Robertson, Kerr, and Henderson cf. also part 3)

Although it is not feasible to determine the molecular refractivity of the caryophyllene alcohol directly owing to its high melting point, it appeared probable that the necessary information might be obtained from the physical properties of certain of its esters which were prepared in the course of this work. cf.p The following figures were therefore determined for the formate and the acetate, and they indicate clearly the tricyclic nature of the caryophyllene radical. The refractivities are calculated according to the expression of Lorentz and Lorenz where

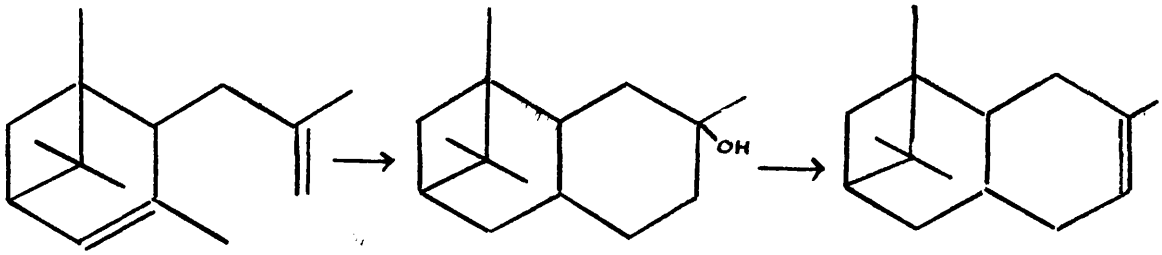
$$\text{molecular refractivity} = MR = \frac{(n^2 - 1)\ M}{(n^2 + 2)\ d}$$

Ester.	t	$d_{4^\circ}^{t^\circ}$	$\eta_D^{t^\circ}$	MR found	MR calc.for $C_{15}H_{25}.R$ Tricyclic	MR for typical $C_{15}H_{25}.R^{ss}$ Bicyclic	MR calc.for $C_{15}H_{25}.R$ Bicyclic
Caryophyllene formate $C_{16}H_{26}O_2$	7°	1.024	1.4998	71.78	71.02	-----	72.75
Caryophyllene acetate $C_{17}H_{28}O_2$	17°	1.003	1.4919	76.37	75.64	78.13	77.37
Exaltation for formate					+.76		----
Exaltation for acetate					+.73		+.76

In the case of the acetate, which melts at 40° , the constants were determined on the supercooled liquid.

It will be observed that the exaltation found in the case of the caryophyllene derivatives is not greater than the similar divergence for a typical bicyclic member.

It is noteworthy that the limonene form of active caryophyllene could readily adapt itself to such ring formation as is indicated by the above results. The course of the reaction and the dehydration of the alcohol to clovene may therefore be represented by the following scheme:-



Lim. caryophyllene Caryophyllene alcohol Clovene

In addition to caryophyllene alcohol, Wallach's hydration method gives rise to a liquid product. This substance was examined and found to consist of an unsaturated hydrocarbon, $C_{15}H_{24}$, b.p.110-114°/9mm.; $d_{40}^{10°}$, 0.9263; $n_{D}^{10°}$ 1.5010; $[\alpha]_{5790}^{16°}$ -19.56°, which evidently differs from β-caryophyllene and is perhaps identical with the tricyclic caryophyllene obtained from the dihydrochloride by the quinoline method (Semmler and Mayer, 1910) which had

b.p.122-123°/13mm., $d_{4^\circ}^{20^\circ}$ 0.927, $n_D^{20^\circ}$ 1.50246, $\alpha_D^{20^\circ}$, -57°.
The properties of clovene given by Wallach (1892) are
b.p.261-263, d$^{18^\circ}$,0.930, $n_D^{18^\circ}$, 1.50066.
It thus seems very probable that these three hydrocarbons are identical.

Wallach(1892) found that caryophyllene alcohol gives a series of halogen derivatives, of which the chloride, $C_{15}H_{25}Cl$, can be readily obtained. This substance can also be regarded as chlorodihydrocaryophyllene. Several experiments on this compound were also carried out, and the results show, as was to be expected, that it behaves as a fully saturated body like the alcohol, and therefore must also be regarded as being tricyclic. It thus becomes of interest to enquire whether hydrogen chloride can be eliminated from this molecule by any of the usual methods, because if this proved to be the case, a new type of tricyclic sesquiterpene would be expected, of which the above mentioned compound would be the hydrochloride.

It was found that this chloride is much more stable than the known hydrochlorides of the sesquiterpene series. Even after prolonged heating in a concentrated alcoholic solution of sodium ethoxide, or with quinoline, practically all the compound was recovered unchanged. ON treatment with sodium acetate in glacial acetic acid solution, however, chlorine was removed from the molecule, but

the product of the reaction in this case proved to be the acetate of caryophyllene alcohol, $C_{15}H_{25}.OAc$. Wallach and Tuttle (1894[27]) mention a caryophyllene acetate, but as no melting point or other data are given, it was not possible to ascertain whether their compound was similar to the above.

Experiments were next directed towards the synthesis of hydroxyl derivatives from caryophyllene corresponding to the bicyclic structure of the hydrocarbon since it has been shown that Wallach's hydration method leads to ring closure. It has already been pointed out that caryophyllene alcohol does not occur in nature; indeed no oxygenated derivatives of caryophyllene have so far been detected in plant sources. But if such compounds should be discovered it might be expected that they would exhibit the bicyclic caryophyllene structure, i.e. be direct hydrates of the hydrocarbon, as is usually the case with other terpenes. It therefore seemed worth while to attempt the synthesis of bodies of this class.

The dihydrochloride of caryophyllene was first prepared and by the action of silver acetate in glacial acetic acid solution a complex mixture of acetates was obtained. This product upon hydrolysis yielded an unsaturated alcohol, $C_{15}H_{25}(OH)$, a saturated glycol, $C_{15}H_{26}(OH)_2$, and some regenerated hydrocarbon. The alcohol

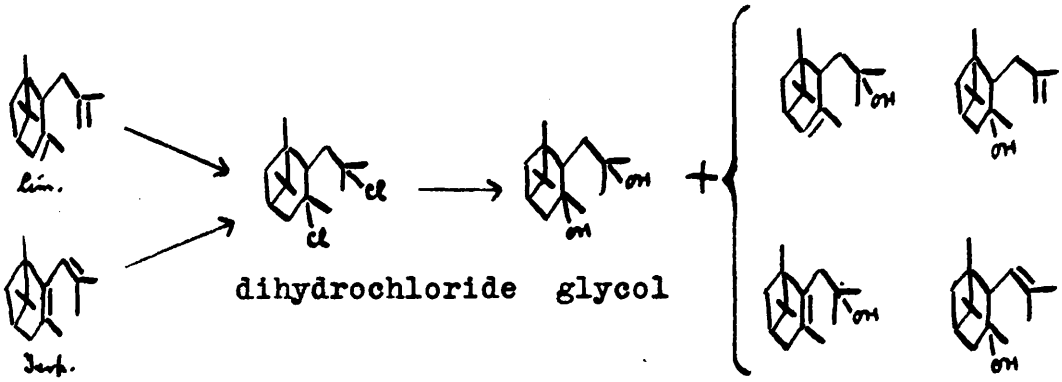
$C_{15}H_{25}(OH)$, which may be termed caryophyllol, has properties corresponding closely to those of a bicyclic sesquiterpene alcohol. Although it reacts with sodium, no ester has yet been obtained by any of the usual methods, which indicates that the alcohol is tertiary. By the action of a chloroform solution of bromine in the cold it is converted into a rather unstable dibromide, $C_{15}H_{24}OBr_2$.

The compound $C_{15}H_{26}(OH)_2$ is quite a stable substance, and is probably a glycol with both hydroxyl groups attached to tertiary carbon atoms. It possesses properties closely similar to those of cadinene glycol, which was prepared in a similar way by Henderson and Robertson, (1924).[20]

The fact that the hydrocarbon product of the reaction gives a good yield of caryophyllene dihydrochloride on treatment with hydrogen chloride indicates that these hydroxyl derivatives also retain the bicyclic caryophyllene structure. Semmler and Mayer (1910) have shown that active caryophyllene can be regenerated from the dihydrochloride in alkaline solution, but not when acid reagents are employed. There was thus some danger that ring closure would occur during the course of the above reaction, which is conducted in acid solution; but the reconversion of the hydrocarbon product to the dihydrochloride proves that such is not the case. This result was obtained by

carefully controlling the temperature conditions of the reaction.

On the basis of Semmler's formulae the formation of these hydroxyl derivatives can be represented as follows although no evidence has so far been obtained to show which of the two possible formulae must be assigned to caryophyllol and indeed it is possible that this alcohol may consist of a mixture of isomeric forms.



dihydrochloride glycol

caryophyllene caryophyllol

It will be observed that only one formula is possible in the case of both the dihydrochloride and the glycol, and these substances are both definite crystalline solids , whereas, the other compounds which may consist of a mixtures of closely related isomers, are liquids which can only be purified by vacuum fractionation.

EXPERIMENTAL.

Preparation of β-caryophyllene .- The caryophyllene used in all the following experiments was prepared from the commercial hydrocarbon supplied by Messrs. Bush & Co., Ltd. Their starting material was Oil Zanzibar Cloves buds , which they steam distilled with alkali to hold back the eugenol , and subsequently gave two alkali washes to remove further small quantities of phenols.

This commercial product was dried over potassium hydroxide, and the pure β-caryophyllene isolated by fractional distillation under diminished pressure. The main product had

b.p. 118-120°/10mm., $n_D^{17°}$, 1.5009; $d_{4°}^{17°}$ 0.9052.

and gave a very good yield of the dihydrochloride, m.p.69°.

Preparation and properties of caryophyllene alcohol.- The most convenient method of preparation was found to be as follows. To 1 litre acetic acid containing 12 cc. sulphuric acid and 40 cc. water, 150 gms. caryophyllene were added and the whole maintained at 80-100° for thirty hours. The product was steam distilled. At first acetic acid and an oil passed over, then the solid alcohol slowly distilled. It was collected and purified by crystallisation from light petroleum at a low temperature. M.p. 94-96°. The yield was about 30 per cent.

The liquid product of the hydration was collect-

-ed by means of light petroleum ether and dried. On removing the solvent and allowing the product to remain Twenty-four hours at 0° , a further quantity of the alcohol separated and was removed. The resulting oil was distilled under diminished pressure and the main product was finally purified by redistillation over sodium in a vacuum. The product consisted of a colourless oil with a pleasant odour, quite different from that of clove oil , and which had

b.p.110-114°/9mm., $d_{4^\circ}^{10^\circ}$, 0.9263, $n_D^{10^\circ}$ 1.5010 $[\alpha]_{5790}^{16^\circ}$ -19.56°

Molecular refractivity = $\frac{n^2-1}{n^2+2} \cdot \frac{M}{d}$ = 64.8

Molecular refractivity calculated for a tricyclic sesqui - terpene, $C_{15}H_{24}$, = 64.4

ANALYSIS

.1720 g. gave .5528 g. CO_2, .1794 g. H_2O .

Found - - - - -	C = 87.7, H = 11.7	per cent
$C_{15}H_{24}$ requires - -	C = 88.2, H = 11.8	per cent

This substance was unsaturated towards bromine. It appears to be identical with clovene.

Caryophyllene alcohol (50 g.) in glacial acetic acid (200 cc.) and 30 per cent hydrogen peroxide (55 cc.) were heated together at 50-55° for fifty-two hours. The solution was then neutralised with sodium carbonate, and the products isolated, when practically the whole of the caryophyllene alcohol was recovered unchanged. M.p. 94°.

On standing in the cold with 1 per cent permanganate the latter was not decolourised, and the alcohol was recovered unchanged. When the alcohol was gradually treated with bromine, both in chloroform solution at room temperature, no absorption or substitution could be detected.

Preparation and properties of other hydroxyl derivatives of caryophyllene.- The dihydrochloride of caryophyllene was prepared by gradually treating caryophyllene (100 g.) in anhydrous ether (100 cc.) with dry hydrogen chloride the temperature of the reaction being kept at 0°. After remaining a further twenty-four hours at 0°, the ether was removed by passing a current of carefully dried air over the surface of the liquid. On reducing the temperature to -20° practically the whole of the liquid crystallised. Recrystallised from ethyl acetate, caryophyllene dihydrochloride had m.p. 69°, $[\alpha]_D^{15°}$, 67° in 2.5 per cent ethyl alcoholic solution. Failure to observe the conditions stated, in particular with regard to temperature, results in a greatly diminished yield of the dihydrochloride.

A solution of caryophyllene dihydrochloride (50 g.) in glacial acetic acid (250 g.) was gradually treated with silver acetate (70 g.). The mixture was shaken for two to three hours at room temperature, and the reaction completed by gently warming on the water bath. On cooling the silver chloride was filtered off, and the

acetic acid neutralised with sodium carbonate. The resulting product consisting principally of acetates, was collected by means of ether and hydrolysed by warming with dilute methyl alcoholic potash for half an hour. After distilling off the alcohol the product was rendered neutral with carbon dioxide and steam distilled. The portion volatile in steam was collected with ether, dried over anhydrous sodium sulphate, and distilled under reduced pressure. After several distillations three principal fractions were obtained:-

(a) b.p. 122-130°/ 10mm.

(b) b.p. 130-140°/10mm.

(c) b.p. 140-150°/ 10mm.

The fraction (a) consisted of a colourless oil which proved to be regenerated caryophyllene. When treated with hydrogen chloride in the manner described above (p.[illegible]) an almost theoretical yield of the dihydrochloride, m.p.69°, was obtained.

The fraction (c) , which represented about twenty per cent of the product, on further purification had

b.p.142-150°/10mm., $d_{4^\circ}^{17^\circ}$, 0.9632, $n_D^{17^\circ}$, 1.5015.

Molecular refractivity = $\frac{n^2 - 1}{n^2 + 2} \cdot \frac{M}{d}$ = 68.03

Molecular refractivity calculated for a bicyclic sesquiterpene alcohol = 68.12.

ANALYSIS

.1352 g. gave .3995g. CO_2, .1362 g. H_2O .

Found - - - - - C = 80.6, H = 11.2 per cent

$C_{15}H_{26}O$ requires - - C = 81.1, H = 11.7 " "

This substance reacts with sodium, but gave no solid derivative when treated in the usual manner with phthalic anhydride, or with phenyl iso-cyanate. It therefore appears to be a tertiary alcohol. On boiling with acetic anhydride dehydration occured yielding a hydrocarbon. The alcohol is unsaturated towards bromine and alkaline permanganate. When slowly treated with bromine at 0°, both in chloroform solution, absorption occured but no substitution was detected. The chloroform was removed under reduced pressure leaving a colourless, oily dibromide.

ANALYSIS

.2159 g. gave .2060 g. AgBr

Found - - - - Br = 40.6 per cent

$C_{15}H_{26}OBr_2$ requires - Br = 41.8 " "

These results are not accurate, as it was not possible to purify the substance completely. On exposure to light the dibromide slowly decomposed. The composition of this compound however, shows clearly that caryophyllol contains one ethylene linkage.

The fraction (b) proved to consist of a mixture of the above alcohol and the hydrocarbon.

A small higher boiling fraction was also obtained, containing a higher percentage of oxygen, which probably consists of a mixture of the above alcohol with a small amount of the glycol referred to below.

The residue from the steam distillation contained a thick brown oil which was repeatedly extracted with ether and ~~and~~ dried. On removing the solvent most of this substance crystallised, and by the addition of a ~~sm~~ small amount of light petroleum, in which the solid was found to be insoluble, the remainder was deposited in minute white needles. The substance was recrystallised from ether as a flocculent mass of minute needles, m.p. 173°. The yield was about three per cent. The composition corresponds with that of caryophyllane glycol, $C_{15}H_{26}(OH)_2$.

ANALYSIS

.1184 g. gave .3236 g. CO_2, .1246g. H_2O .

Found - - - - C = 74.5, H = 11.7 per cent

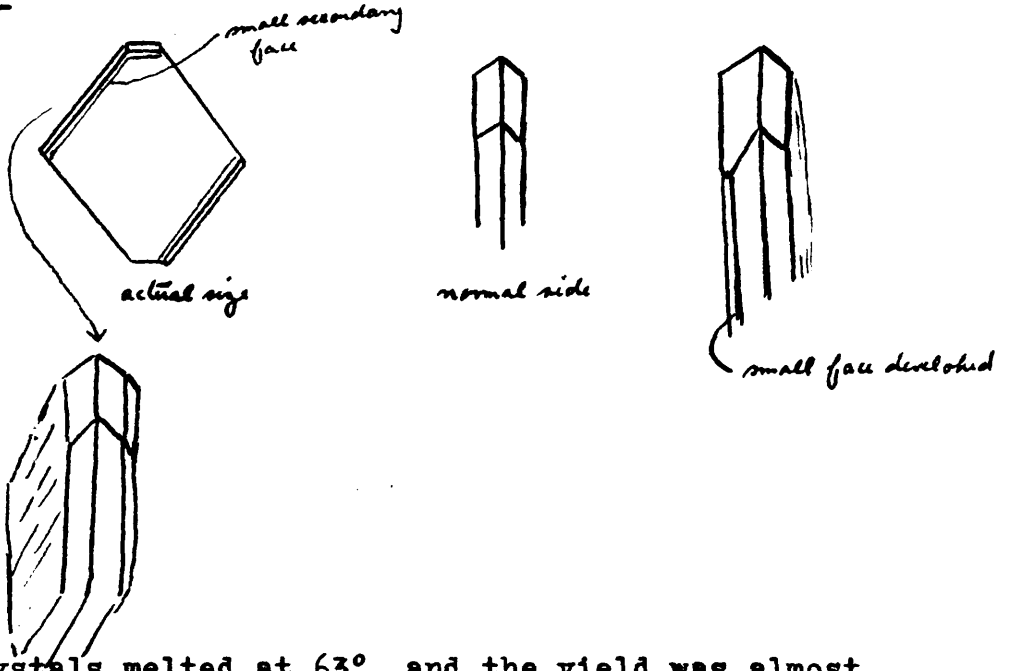
$C_{15}H_{28}O_2$ requires - C = 75.0, H = 11.7 " "

The substance is very soluble in alcohol, slightly soluble in ether, and almost insoluble in light petroleum. It does not decolourise bromine or alkaline permanganate solution.

Reactions of caryophyllene chloride (or chlorodihydro - caryophyllene).-

The chloride was prepared from caryophyllene alcohol by the

action of phosphorous pentachloride (Wallach and Walker, 1892.).[53] It was purified by crystallisation from light petroleum ether, from which solvent it separated in large prisms, which in some cases were beautifully formed, as below.-



The crystals melted at 63°, and the yield was almost theoretical.

ANALYSIS

.1837 g. gave .1113 g. AgCl

Found - - - Cl = 14.99 per cent

$C_{15}H_{25}Cl$ requires - Cl = 14.75 " " .

A portion of the chloride was refluxed at 100° with a concentrated solution of sodium ethylate for twelve hours. No action took place and the chloride was recovered unchanged Another portion was heated to 210° in quinoline solution for three hours, but even after that time no action occured

and the compound was recovered unchanged.

A third portion (20 g.) was dissolved in glacial acetic acid (150 cc.) and anhydrous sodium acetate (19 g.) gradually added. The solution was boiled for three hours. After one hour sodium chloride began to be deposited. On cooling the product was diluted with water and extracted with light petroleum. After removing the solvent from the dried extracts, the product was distilled under reduced pressure, when a colourless oil was obtained, b.p.149-152°/10mm., which was saturated towards bromine. When mixed with light petroleum ether and cooled to -20° , a solid mass of small white crystals separated which on purification melted at 40°. The yield was nearly theoretical, This substance is fairly soluble in alcohol and in light petroleum. Acid ethyl alcoholic hydrolysis yielded ethyl acetate, and by hydrolysis with methyl alcohol -ic potash a theoretical yield of caryophyllene alcohol, m.p. and mixed melting p. 95, was obtained. The substance is therefore caryophyllene acetate, $C_{15}H_{25}O.CO.CH_3$.

ANALYSIS

.1890g. gave .5324 g. CO_2,, .1793 g. H_2O

Found - - - C = 76.8, H = 10.5 per cent

$C_{17}H_{28}O_2$ requires - C = 77.2, H = 10.6 " " .

It was found that the acetate could be supercooled to 17° with care, and then had $n_D^{17°}$ 1.4919, $d_4^{17°}$, 0.9961. (cf.p.5)

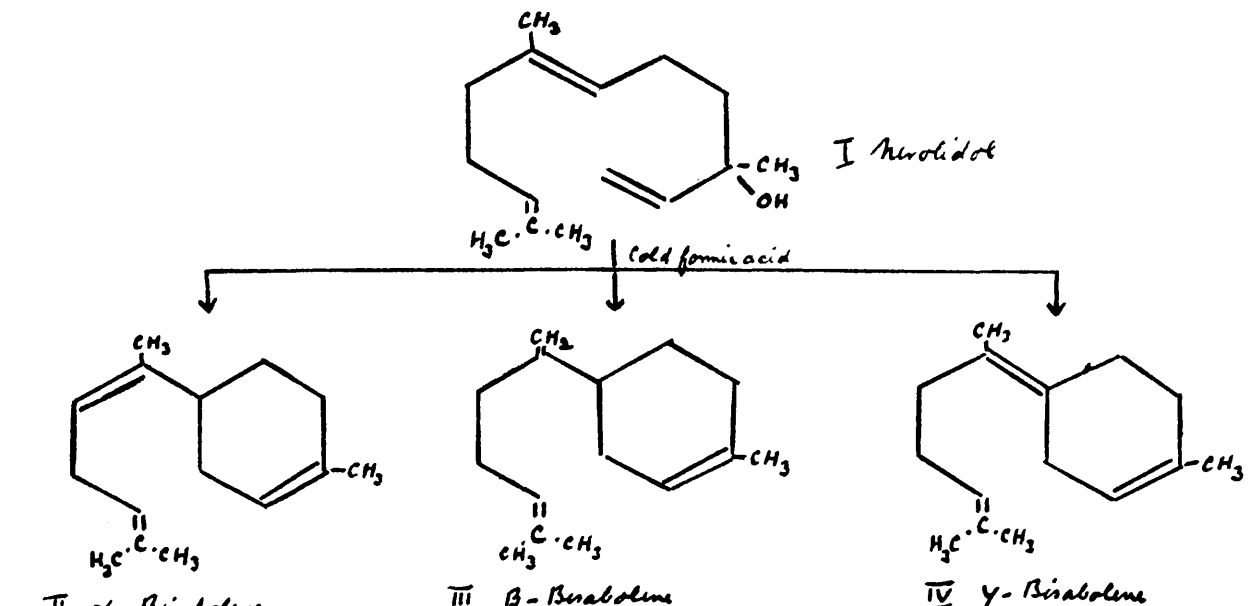
PART 3.

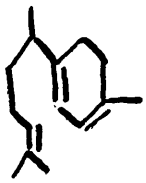
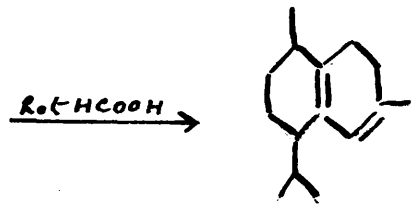
RING FORMATION IN THE SESQUITERPENE SERIES BY MEANS OF ACID REAGENTS.

Part 3.

RING FORMATION IN THE SESQUITERPENE SERIES BY MEANS OF ACID REAGENTS. (THE ACTION OF FORMIC ACID ON CERTAIN SESQUITERPENES.)

The action of anhydrous formic acid as a means of effecting ring closure in the sesquiterpenes is now well established. Semmler and Spornitz (1913) [4] ascertained the transition of the aliphatic sesquiterpene from Java Citronella oil into a monocyclic isomer by the action of concentrated formic acid. Ruzicka and Capato (1925) [38, 5] in their synthesis of bisabolene (II, III, r IV.) have now shown that the action of formic acid in the cold closes one ring in the nerolidol structure (I), whereas, by more prolonged action with the same reagent at a higher temperature, the closure of two rings is effected, a hexahydrocadalene (VI) being thus produced. They also observed the production of alcohols as intermediate bodies.

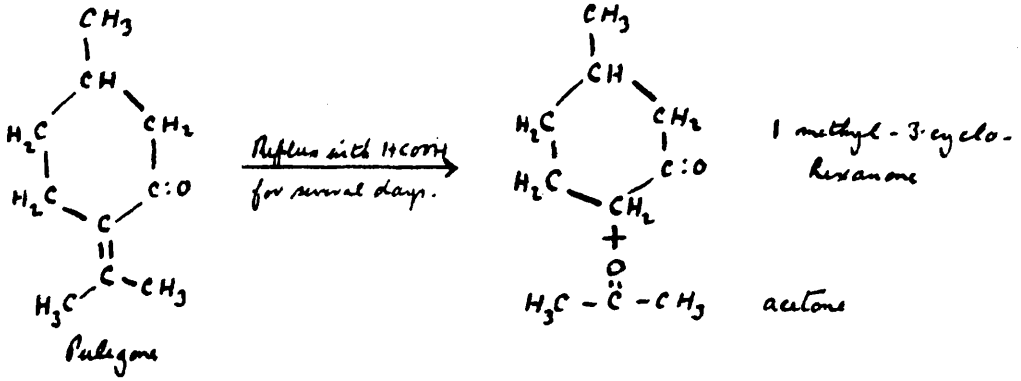


Bisabolene   

V Hypothetical intermediate product.

VI Hexahydrocadalene

This reagent may also act in another way, as was shown by Wallach (1896)[56] who found that on refluxing pulegone with anhydrous formic acid for several days acetone and 1-methyl-3-cyclo-hexanone resulted. Formic acid may therefore be of use in determining the presence of an iso-propylidene grouping in the molecule.



It is noteworthy, however, that in the case of bisabolene and nerolidol the iso-propylidene group is not displaced, but ring formation occurs instead with a rearrangement of the double bonds in the molecule.

The following work was undertaken firstly in order to determine whether Wallach's method would indicate the presence of an iso-propylidene grouping in the molecule

of caryphyllene, cadinene, or cedrene. The results in this direction were entirely negative. The action of formic acid, however, was found to bring about certain interesting molecular rearrangements in these sesquiterpenes, of the type described by Ruzicka and Capato, and Semmler.

It was shown (Robertson, Kerr, and Henderson 1925) that caryophyllene on treatment with formic acid gives in about 35 per cent yield a compound, $C_{16}H_{24}O_2$, which proved to be the formic ester of caryophyllene alcohol, together with a mixture of hydrocarbons, probably consisting of clovene and unattacked caryophyllene. On hydrolysis of the ester, caryophyllene alcohol was obtained.

From the work previously described (cf.p.) it is obvious that this is a case of ring formation, the sesquiterpene passing from the bicyclic caryophyllene structure to the tricyclic clovene structure. The existance of the formic ester also provides a clue to the mechanism of the isomerisations brought about by formic acid in terpene chemistry and makes it reasonable to suggest that intermediate esters of formic acid are first formed but break down under the conditions of the experiment so that a molecule of formic acid is eliminated to give a new hydrocarbon.

It has also been found that this reaction of formic acid with caryophyllene can proceed if the reagents are allowed to stand together for several days in the cold.

The yield of the ester is the same. In the case of cadinene and cedrene the hydrocarbon was not appreciably attacked in the cold, but when heated for some time with concentrated formic acid isomeric hydrocarbons were produced.

The chief product from cadinene consisted of a hydrocarbon, or a mixture of hydrocarbons, b.p.118-124°/9mm, of the formula $C_{15}H_{24}$, which did not form a stable hydrochloride, together with some unchanged cadinene. On heating cadinene in an autoclave, Semmler and Jakubowiez (1914)[57] obtained a substance, b.p. 120-130°/?mm, d.0.9025, n_D 1.50829 which they considered to be a monocyclic sesquiterpene mixed with cadinene. The product obtained in the present experiments agrees closely with the above in its physical properties, but it is probable that iso-cadinene constitutes the bulk of this product.

Cedrene yielded as chief product an isomeric unsaturated hydrocarbon, b.p. 114-118°/9mm., some unchanged cedrene, and a small fraction of higher boiling point. As fractional distillation was the only method of purification, it is unlikely that these substances are free from unattacked cedrene. The presence of alcoholic compounds is suspected in the higher fractions.

EXPERIMENTAL.

The reaction between formic acid and caryophyllene.- β-caryophyllene (50g.) and anhydrous formic acid (50g.) were mixed together. After a short time a vigorous reaction commenced, and the mixture was kept cool with a stream of cold water. Finally the mixture was allowed to stand for several days with occasional shaking. It was then neutralised with sodium carbonate, the product extracted with ether and dried. After removing the solvent, the resulting oil was distilled under diminished pressure. After several distillations a main fraction was isolated which had

b.p.142-146°/10mm., $n_D^{?°}$,1.4998, $d_{4°}^{?°}$,1.025

(cf. p.)

This fraction consisted essentially of the formate of caryophyllene alcohol, as is shown by the following analysis.

ANALYSIS

.2458g. gave .6959 g. CO_2, .2216 g. H_2O.

Found - - - C = 77.21, H = 10.02 per cent

$C_{16}H_{24}O_2$ requires - C = 76.8 , H = 10.4 " "

Hydrolysis of this ester gave a practically quantitative yield of caryophyllene alcohol, m.p. 95°.

This method affords a convenient preparation of caryophyllene alcohol from the hydrocarbon.

Action of formic acid on cadinene.- Cadinene was prepared from the dihydrochloride m.p.118°, by regeneration with anhydrous sodium acetate in glacial acetic acid solution. The pure cadinene had

b.p. 134-136°/10mm., $d_{4^\circ}^{20^\circ}$, 0.9189, $n_D^{20^\circ}$ 1.5079, $[\alpha]_{5461}^{18^\circ}$ -125°.

Equal quantities of cadinene and 99 per cent formic acid were heated together under reflux at 100° for forty hours. The liquid slowly became red. After neutralisation with sodium carbonate the products were extracted with ether and treated with alkali. The final products were distilled under diminished pressure. After several distillations two main fractions were obtained

(a) b.p. 118-124°/9mm.

(b) b.p. 126-134°/9mm.

together with some brown resinous substances.

The fraction (a) consisted of an unsaturated hydrocarbon $C_{15}H_{24}$, which had

$d_{4^\circ}^{17^\circ}$, 0.9086, $n_D^{14^\circ}$, 1.5010.

ANALYSIS

.1799 g. gave .5758 g. CO_2, .1954 g. H_2O

Found - C = 87.28, H = 12.07 per cent

$C_{15}H_{24}$ requires C = 88.16, H = 11.85 per cent.

When this substance was treated with dry hydrogen chloride

in glacial acetic acid solution, no solid hydrochloride was formed.

The fraction (b) consisted chiefly of unchanged cadinene.

Action of formic acid on cedrene.- Cedrene was purified by distillation over sodium, and had

b.p. 122-124°/9mm., $d_{4°}^{20°}$ 0.9361, $n_D^{21°}$ 1.5005

It was treated with formic acid in the same way as cadinene and the products worked up as before. After a large number of distillations under reduced pressure, the following fractions were obtained

(a) b.p. 114-118°/9mm.

(b) b.p. 118-130°/9mm.

(c) b.p. 130-135°/9mm.

The fraction (a) comprising about 50 per cent of the product consisted of an unsaturated hydrocarbon, $C_{15}H_{24}$, which had

$d_{4°}^{20°}$, 0.9333, $n_D^{21°}$ 1.4988.

ANALYSIS

.1652 g. gave .5325 g. CO_2, .1774 g. H_2O

Found - - - C = 87.90, H = 11.93 per cent

$C_{15}H_{24}$ requires - C = 88.24, H = 11.76 per cent

No derivative could be obtained from this substance, but from the physical constants given above it appears to consist of a tricyclic hydrocarbon.

The fraction (b) consisted chiefly of anattacked cedrene. The fraction (a) appears from its analysis to contain alcoholic bodies as well as hydrocarbons, but only a a small quantity was available for examination.

ANALYSIS

.1168 g. gave .3634 g. CO_2, .1182 g. H_2O .

Found - - C = 84.84, H = 11.25 per cent

In conclusion, I wish to express my thanks to my Chief and Supervisor, Professor G.G.Henderson, for his continued interest and advice during the progress of this work, and for the great facilities he has afforded me in carrying it out.

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